

## Cross-sex hormone administration changes pain in transsexual women and men

Anna Maria Aloisi <sup>a,\*</sup>, Valeria Bachiocco <sup>a,b</sup>, Antonietta Costantino <sup>c</sup>, Rita Stefani <sup>d</sup>,  
Ilaria Ceccarelli <sup>a</sup>, Alessandro Bertaccini <sup>c</sup>, Maria Cristina Meriggiola <sup>c</sup>

<sup>a</sup> Department of Physiology, Neuroscience and Applied Physiology Section, University of Siena, Via A. Moro, 2, 53100 Siena, Italy

<sup>b</sup> Anaesthesia and Intensive Care Unit, S. Orsola Hospital, Bologna, Italy

<sup>c</sup> Obstetrics and Gynaecology Unit, S. Orsola Hospital, Interdepartmental Centre for Sexual Health, University of Bologna, and M.I.T., Bologna, Italy

<sup>d</sup> Anaesthesia and Intensive Care Unit, S. Agostino-Estense New Hospital, Modena, Italy

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### Abstract

Chronic pain is gender-related, since there is a clear predominance of one sex with respect to the other in most pain syndromes. Gonadal hormones are known to affect the occurrence and incidence of pain. Transsexuals receive cross-sex hormones to develop and maintain somatic characteristics of the opposite sex: male to female transsexuals (MtF) are administered estrogens and anti-androgens, while female to male transsexuals (FtM) are administered androgens. Hence, these subjects represent a model to study the relationship between sex hormones and pain. Questionnaires dealing with sociodemographic data and pain (occurrence, frequency, duration, intensity, location and associated symptoms) were administered to both MtF and FtM transsexuals under hormone treatment for sex reassignment for at least 1 year. Forty-seven MtF and 26 FtM completed the questionnaires. Fourteen of the 47 MtF (29.8%) reported painful conditions, which in 11 subjects were not present before the beginning of hormone treatment. Pain consisted mainly of headaches and breast and musculoskeletal pain. Five subjects suffered from more than one pain condition. Sixteen of the 26 FtM (61.5%) reported pain. In 11 subjects, the pain was present before the beginning of hormone intake, and in 6 of them it improved after testosterone administration. These data suggest that marked changes in sex hormones affect the occurrence of pain in a high percentage of humans but not in all of them. Whether these effects are due to peripheral or central actions of sex steroids is unknown.

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### 1. Introduction

In most pain syndromes studied, women have a different risk of developing chronic pain than men of the same age (LeResche et al., 2005; Wiesenfeld-Hallin, 2005). Differences in sex steroid levels, receptors and/or sites of action may play a role in these sex differences (Aloisi, 2003; Craft et al., 2004). Androgens, higher in

males, appear to protect against the development of chronic pain in humans, and testosterone was found to have analgesic effects on experimental pain (Ceccarelli et al., 2003; Aloisi et al., 2004; Hau et al., 2004). Contradictory results have been reported for estrogens. In both humans and experimental animals, estrogens have been found to have both analgesic and hyperalgesic effects depending on the experimental conditions (Aloisi and Bonifazi, 2006; Smith et al., 2006).

Transsexualism or gender identity disorder is a nosologic condition in which an otherwise normal person feels that she/he belongs to the opposite sex to which

\* Corresponding author. Tel.: +39 0577234103; fax: +39 0577234037.  
E-mail address: aloisi@unisi.it (A.M. Aloisi).

she/he was born (see Michel et al., 2001 for a review). For this reason, the masculine transsexual (male to female, hereafter referred to as MtF) demands feminization of his body, while the feminine transsexual (female to male, FtM) aspires to masculinization of her body.

Transsexuals undergo a standard cross-sex hormone treatment, which in most cases is continued for life. Despite the differences in dosages, routes of administration, basal conditions of each subject and the responses to endocrinological treatment, the changes occurring in the male or female body are constant and due to the agonistic or antagonistic actions of the sex hormones used. Estrogens are the cornerstone of the feminization treatment of MtF transsexuals. To potentiate the effects of estrogens, subjects often take anti-androgens (i.e. cyproterone acetate) which lower the endogenous testosterone level and block its binding to the androgen receptors. Testosterone is the key hormone in the treatment of FtM transsexuals, and a progestin is sometimes added to stop menstrual bleeding.

The effects induced by sex steroids in transsexuals are reported in recent articles (Levy et al., 2003; Moore et al., 2003; De Cuypere et al., 2005; Gooren, 2005). Some of these effects are considered positive depending on the target sex (i.e. gynecomastia and decreased hair growth in MtF and hirsutism and breast atrophy in FtM), while others are negative (venous thrombosis and depression in MtF and increased hematocrit in FtM).

The changes in pain have never been described in detail. Thus, the aim of the present study was to evaluate pain changes after long-term estrogen/androgen treatment in transsexuals. To collect background information on the current sensitivity to sensory stimuli (nociceptive and thermal) and the pain history (personal and familial), we conducted a two-part semi-structured interview to MtF and FtM transsexuals under hormone treatment for sex reassignment. If chronic pain was reported, a standardized questionnaire was given to define some features of the pain (occurrence, frequency, duration, intensity, location and associated symptoms). Since our hypothesis was that estrogens are pro-nociceptive and androgens are analgesic, we expected different modulation of the painful conditions in males exposed to prolonged estrogen supplementation (MtF) with respect to those present in females exposed to prolonged androgen supplementation (FtM).

## 2. Methods

### 2.1. Subjects and procedures

To study the effects of hormone treatments on pain, we contacted transsexuals attending the MIT (Movimento Identità Transessuale) Centre in Bologna between December 2003 and December 2005. Sex reassignment involves various legal and medical steps that have to follow a determined course.

In the MIT Centre, the HBIGDA guidelines are followed for diagnosis and treatment (HBIGDA, 2001). The MIT Centre has specialists who initiate the hormone treatments and carry out the periodic controls. These periodic visits are obligatory but their scheduling usually complies with personal and/or logistic reasons, so that it is not easily standardized. Thus, we asked *all* transsexuals (MtF and FtM) in treatment for at least one year to be included in the study without any selective criteria. Seventy-three Caucasian subjects, 47 male to female (MtF) and 26 female to male (FtM) transsexuals, entered the study. All subjects fulfilled the DSM-IV diagnostic criteria for gender identity disorder (American Psychiatric Association, 1994). In all the MtF transsexuals, hormone treatment consisted of cyproterone acetate, an oral progestagen with strong anti-androgenic activity, combined with oral, injectable or transdermal estradiol. In the FtM subjects, testosterone treatment consisted of a mixture of testosterone esters (testosterone enanthate + testosterone propionate) injected intramuscularly, testosterone enanthate or transdermal testosterone.

All participants were informed about the nature of the study (i.e. to compare the incidence of chronic pain in transsexuals during hormone treatments with the period before hormone treatment) and gave written informed consent. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Siena, and was conducted in accordance with the guidelines proposed in the Helsinki Declaration. The instruments to collect relevant information (the same semi-structured interview and questionnaires for all subjects) were administered at the end of the clinical assessment and always in the same setting (a visiting room for out-patients) by the same physician (MCM), an expert in the management of transsexuals and specifically trained. Questionnaires were administered as self-report measures.

### 2.2. Questionnaires

A two-part semi-structured interview was carried out with *ad hoc* and standardized questionnaires. The first part of the interview dealt with the socio-demographic data, the duration of hormone treatment, the kind of hormones taken, the kind of surgery (if done), and the physical changes occurring after the hormone administration. Other questions addressed possible hormone-related changes in the subjects' sensitivity to painful and thermal stimuli (warm and cold) and their ability to tolerate them. The subjects were then asked to report if they were suffering any kind of pain in the last few days, weeks, months or years. If pain was described as persistent or occurring recurrently for a period longer than 4 months (chronic pain), subjects were asked to participate in the second part of the interview, which concerned the clinical history, past and present pain history, and pain history of the family. A domain-linked questionnaire explored the temporal relationship between the pain and the hormone intake (if pain was present before or arose after hormone assumption), its severity with respect to the hormone therapy (if the pain was getting better or worse after the start of therapy) and its temporal profile (how many times it occurred in a day, a week, a month, a year; how long the pain lasted when it appeared). Other questions concerned what made the pain worse and how much the pain influenced daily activities.

For each type of pain, the validated Italian version (Maiani and Sanavio, 1985, 1989) of the full-scale McGill Pain Questionnaire (MPQ) (i.e. 78 descriptors) was administered. The MPQ measures the components of pain (Melzack and Casey, 1968; Melzack, 1975). The interviews and questionnaires were evaluated by two researchers, different from the examiner, and were quantified according to the answer format (category or number). These researchers were blind to the transsexuals' gender.

The subjects were also asked to mark their pain sites on a body map. Lastly, a battery of Visual Analogue Scales (0–10) was used to rate the intensity of pain at various times according to the anchor words: no pain/the highest pain during: (a) the last 24 h (VAS<sub>1</sub>), (b) the last week (VAS<sub>2</sub>), (c) the pain attacks (VAS<sub>3</sub>), (d) the night in general (VAS<sub>4</sub>).

### 2.3. Hormone plasma levels

Serum levels of the hormones (testosterone, estradiol, FSH and LH) were measured only in subjects that carried out all phases of the sex reassignment in the MIT Centre in Bologna. It was possible to obtain hormonal data for only some of the other subjects who started the hormone treatments in other places. Hormone levels were determined by the immunoradiometric method using commercial kits (Adaltis Italia, Bologna, Italy) in the centralized service of the Sant'Orsola Hospital (Bologna).

### 2.4. Analysis

In subjects for whom hormone values were available, Student's *t*-test was used to identify significant differences between the hormone levels determined before the start of hormonal treatment and during stable treatment. Significance was accepted with  $p < 0.05$ . The questionnaire data were analyzed by grouping the subjects (MtF and FtM separately) into those suffering chronic pain (persistent or recurrent pain lasting longer than 4–6 months) and those without chronic pain (suffering only sporadic/physiological pain episodes). Basic statistics (mean, SEM, percentages) were computed when required. The McGill Pain Questionnaire ratings were calculated using the Pain Rating Index rank method (PRI; Melzack, 1975) for each component (sensory, affective, evaluative, miscellaneous). Data are reported as the sum of rank values of the descriptors (Pain Rating Index rank Total, PRIrT) and as percentage for each component.

## 3. Results

### 3.1. Clinical

Forty-seven MtF and 26 FtM completed the questionnaires (age range 25–40 years); all subjects reported that the body changes occurred as expected after the start of hormone treatment. Indeed, male to female (MtF) subjects reported an increase in breast size and hip circumference, while female to male (FtM) subjects reported a deepening of the voice, body hair and beard growth, and an increase in waist circumference.

### 3.2. Hormones

Table 1 includes data on the serum hormone levels determined in 25 of the 47 MtF and in 19 of the 26 FtM before the start of treatment and during the clinical assessment, when the interview was carried out. Although it was not possible to obtain data at the same time after the start of treatment in all subjects, the second value refers to steady-state conditions in the period of hormone peaks.

In the MtF subjects, serum estradiol levels were significantly increased with respect to baseline levels ( $p = 0.048$ ) after estrogen and anti-androgen intake; in contrast, testosterone, LH and FSH were significantly lowered ( $p < 0.01$  for all). In FtM subjects, serum testosterone levels were significantly raised with respect to baseline levels ( $p < 0.01$ ), while estradiol and LH levels were significantly decreased ( $p < 0.03$  and  $p < 0.02$ , respectively) and there were no significant changes in serum FSH levels.

### 3.3. Results of questionnaires

The main results of the questionnaires are described in the following sections. Subjects were divided into those with pain and those without pain. The number of subjects who underwent surgery and the average duration of hormone treatment (in months) are also specified. All data concerning the qualitative characteristics of the sensations elicited by acute pain episodes and thermal stimuli refer to subjective evaluations.

### 3.4. Male to female subjects (MtF)

All contacted subjects entered the study. As reported in detail in Tables 2 and 3, 14 of the 47 MtF transsexuals reported ongoing pain (Pain group, 29.8%), while 33 declared that they were not experiencing any kind of chronic pain (Pain-free group, 70.2%). The duration of hormone administration in these two groups was: Pain group  $55.7 \pm 25.5$  months; Pain-free group  $37.7 \pm 5.8$  months. Only 12 of the 47 subjects underwent breast surgery and/or vaginoplasty, and only one of these subjects was in pain.

#### 3.4.1. MtF Pain group

Eleven of the 14 subjects belonging to the Pain group specified that the pain started after the beginning of hormone intake (headache appeared in 3 subjects, breast pain in 11, musculoskeletal pain in 2 and an unusual post-surgical pain in one); the other 3 subjects were already experiencing pain before the start of treatment (2 headache, 1 musculoskeletal pain). As reported in Table 3, 9/14 of these subjects described a single type or single location of pain, while the others (5/14) reported more than one type of pain.

Table 1  
Hormone serum levels determined in transsexual male to female (MtF) and female to male (FtM) subjects

Mean $\pm$ SE	Baseline MtF	Post Txt No. 25	
E (pg/mL)	32 $\pm$ 2	145 $\pm$ 43*	$p = 0.048$
T (ng/mL)	5.7 $\pm$ 0.5	0.8 $\pm$ 0.3*	$p < 0.01$
LH (IU/mL)	4.8 $\pm$ 0.5	0.4 $\pm$ 0.2*	$p < 0.01$
FSH (IU/mL)	3.6 $\pm$ 0.2	0.5 $\pm$ 0.1*	$p < 0.01$
	FtM	No. 19	
T (ng/mL)	0.67 $\pm$ 0.1	7.54 $\pm$ 0.9*	$p < 0.01$
E (pg/mL)	113 $\pm$ 17	67 $\pm$ 8*	$p = 0.037$
LH (IU/mL)	12.1 $\pm$ 2.6	6.7 $\pm$ 1.5*	$p = 0.022$
FSH (IU/mL)	6.2 $\pm$ 0.9	4.6 $\pm$ 0.6	

Estradiol (E), testosterone (T), LH and FSH were determined before the start of the hormonal treatment (baseline) and during stable treatment (Txt).

\* Student's *t*-test  $p < 0.05$ .

In general, all subjects reported that acute pain episodes were getting more frequent and their duration was progressively increasing after the start of treatment. They also reported that they perceive pain earlier and more easily and their tolerance of painful experiences was decreased by hormone treatment. Moreover, subjects reported being more sensitive to and less tolerant of high or low temperatures.

**3.4.1.1. Headache.** Five MtF suffered from headaches. Headaches appeared several times during the week, sometimes lasting all day. Each subject marked more than one pain location on the head map. Environmental stimuli, especially light and sounds, exacerbated pain severity, and subjects reported that sometimes pain was so great they could no longer carry out daily activities. Pain greatly increased after hormone intake in the two subjects in which it was already present before treatment. The McGill Pain Rating Index rank Total (PRIr-Tot) was  $53.4 \pm 6.7$  (Table 4); in particular, the sensory (%  $74.2 \pm 7.7$ ) and evaluative components (%  $76 \pm 16.0$ ) had higher values than the others (affective  $54.2 \pm 15.7$ ; miscellaneous  $63.4 \pm 13.3$ ). The highest score in the VASs was during the crisis (VAS<sub>3</sub>:  $6.5 \pm 1.5$ ).

**3.4.1.2. Breast pain.** This kind of pain was present in 11 of the 14 MtF who reported chronic pain. They all stated that it arose after the start of hormone treatment. It

Table 3  
Males to females: number of subjects suffering chronic pain and kind of pain

Pain	Subjects $n = 14$
<i>Single pain or site</i>	<i>N=</i>
Headache	1
Breast	7
Musculoskeletal	1
<i>Multiple pains or site</i>	
Headache + breast	2
Headache + musculoskeletal	1
Breast + musculoskeletal	1
Headache + breast + visceral	1

Subjects are divided depending on the kind and number of pains.

was mainly unilateral (6 subjects) and continuous, and was exacerbated by rubbing and touching.

The Pain Rating Index rank Total (PRIrTot, Table 4) was  $14.7 \pm 2.8$ , with the evaluative component (%  $27.3 \pm 8.2$ ) having higher scores than the others (sensory %  $14.9 \pm 4.6$ ; affective %  $5.8 \pm 3.8$ ; miscellaneous %  $16.7 \pm 5.6$ ). Four subjects did not select any adjective in the affective class.

**3.4.1.3. Other kinds of pain.** Three of the 14 MtF with chronic pain reported severe and diffuse musculoskeletal pain. This type of pain was present before the start of hormone therapy in one subject but greatly increased afterwards. Movements and posture shifts greatly worsened pain. The Pain Rating Index rank Total (PRIrTot, Table 4) was  $29.0 \pm 22.7$ , with the sensory component (%  $61.0 \pm 16.4$ ) having higher values than the others (evaluative %  $46.7 \pm 17.6$ , affective %  $36.0 \pm 32.0$ , miscellaneous %  $47.3 \pm 28.8$ ). In addition to headache and breast pain, an extremely severe and unusual post-surgical pain (orchiectomy for cancer, a rare kind of pain) was reported by another MtF subject.

#### 3.4.2. MtF Pain-free group

This group includes all MtF subjects (33/47, 70.2%) who did not report chronic pain. Nevertheless, some of them (6/33) reported that they perceive pain earlier and more easily with respect to the period before hormone treatment; in fact, acute pain episodes recurred more frequently than in the past, with the painful sensation lasting longer than usual. Independently of changes in pain, the sensitivity to thermal stimuli (both warm

Table 2  
Number of subjects belonging to the different groups divided for the presence or absence of pain both before and after the beginning of hormonal treatment

Subjects	Total number $N=$	Pain before treatment $N=$	Pain after treatment $N=$	Pain group $N=$	% subjects in pain	Pain free group $N=$	% subjects without pain
MtF	47	3	11	14	29.8	33	70.2
FtM	26	14	2	16	61.5	10	38.5

Table 4  
Males to females: results of the MPQ and VAS

Pain	Subjects	McGill Pain Questionnaire (MPQ)					Visual Analogue Scale (VAS 0–10)			
		Total PRIrTot	Sensory %	Affective %	Evaluative %	Miscellaneous %	VAS <sub>1</sub>	VAS <sub>2</sub>	VAS <sub>3</sub>	VAS <sub>4</sub>
Headache	5	53.4 ± 6.7	74.2 ± 7.7	54.2 ± 15.7	76 ± 16.0	63.4 ± 13.3	2.6 ± 0.9	5.2 ± 1.4	6.5 ± 1.5	2.5 ± 1.04
Breast	11	14.7 ± 2.8	14.9 ± 4.6	5.8 ± 3.8	27.3 ± 8.2	16.7 ± 5.6	4.1 ± 0.8	4.2 ± 0.8	3.5 ± 1.2	4.4 ± 0.6
Musculoskeletal	3	29.3 ± 22.7	61.0 ± 16.4	36.0 ± 32.0	46.7 ± 17.6	47.3 ± 28.8	4.7 ± 2.4	5.3 ± 2.7	4.3 ± 2.6	3.7 ± 1.4
Visceral referred	1	42	78.5	7.1	100	17.6	0	10	10	0

Data refer to each kind of pain. MPQ, PRIrTot = Pain Rating Index rank Total. The total score is obtained summing the rank values of the adjectives chosen. Separate score for the sensory, affective, evaluative and miscellaneous classes is also computed. For each class, the percentage with respect to maximum values has been calculated. VAS<sub>1</sub> = during the last 24 h VAS<sub>2</sub> = during the last week VAS<sub>3</sub> = during attacks VAS<sub>4</sub> = during the night.

and cold temperatures) was reported to be enhanced in all MtF belonging to this group, while their ability to tolerate the stimuli was reported to be decreased.

### 3.5. Female to male subjects (FtM)

All contacted subjects entered the study. Sixteen of the 26 FtM subjects reported being in pain (Pain group, 61.5%, Table 2), whereas 10 reported being pain-free (Pain-free group, 38.5%). The average duration of hormone treatment was: Pain group  $33.5 \pm 7.2$  months; Pain-free group  $43.3 \pm 10.1$  months. All but six of the 26 FtM subjects had undergone surgery of the uterus and ovaries (hystero-annexiectomy) with mastectomy; of these 20 subjects, 11 belonged to the chronic pain group.

#### 3.5.1. FtM Pain group

Sixteen of the 26 FtM were suffering chronic pain. As reported in detail in Table 5, the most common painful conditions were headache (present in 13 subjects), musculoskeletal pain (present in 7 subjects) and visceral referred pain (present in 2 subjects); 10/16 FtM reported only one kind of pain, while the others (6/16) reported more than one kind of pain. Most of the subjects belonging to the Pain group (14/16) stated that pain was already present before the beginning of the hormone treatment.

**3.5.1.1. Headache.** Headache was present in 13 of the 16 FtM subjects in pain; the majority of them (10/13) reported that the pain was already present before hor-

mone treatment and they all stated that their relatives also suffered from this pathology. Most of them (7/13 subjects) marked a single pain location on the head map.

In the 10 subjects with headache before the hormone therapy, testosterone intake improved pain in six, did not change it in three and increased its severity in one. Subjects who said that pain was getting better reported a decrease in the number of pain attacks (from several times per week to once a month or less); furthermore, they stated that the headache duration was usually shorter than before (no more than 1–2 h).

In the three subjects in whom headache was *not* present before the start of treatment, this pathology was absent in the clinical history of the family and the pain features worsened progressively. These subjects indicated more than one site of pain on the head map and stated that pain sometimes impeded usual activities.

The Pain Rating Index rank Total (PRIrTot, Table 6) was  $20.1 \pm 4.3$ , with the sensory (%  $30.5 \pm 6.1$ ) and evaluative components (%  $31.0 \pm 5.6$ ) exceeding the others (affective  $14.2 \pm 5.2$ ; miscellaneous  $21.3 \pm 5.4$ ). The highest score in the VASs was during the attacks ( $4.9 \pm 1.01$ ).

**3.5.1.2. Musculoskeletal pain.** Musculoskeletal pain was present in 7 of the 16 subjects. In 2 of them, it appeared after the hormone treatment. Pain severity was high, with very frequent pain attacks or continuous pain. Indeed, in most subjects, pain usually occurred several times per day (5 subjects), while in a few cases (2 subjects) it occurred only several times per week. Movements, posture changes and anxiety enhanced pain.

The Pain Rating Index rank Total (PRIrTot, Table 6) was  $29.5 \pm 5.4$ , with the evaluative (%  $51.4 \pm 13.0$ ) and sensory components (%  $43.5 \pm 7.5$ ) having higher values than the others (affective  $29.5 \pm 9.1$ ; miscellaneous  $26.8 \pm 8.8$ ). The VAS scores were high in the ratings referring to the attack ( $7.2 \pm 1.7$ ) and during the last week ( $6.8 \pm 1.5$ ).

#### 3.5.2. FtM Pain-free group

The 10 FtM subjects *not* suffering chronic pain reported no change in the occurrence or perception of

Table 5  
Females to males: number of subjects suffering chronic pain and kind of pain

Pain	Subjects <i>n</i> = 16
<i>Single pain or site</i>	
Headache	<i>N</i> = 8
Musculoskeletal	1
Visceral	1
<i>Multiple pains or site</i>	
Headache + musculoskeletal	5
Musculoskeletal + visceral	1

Subjects are divided depending on the kind and number of pains.

Table 6  
Females to males: results of the MPQ and VAS

Pain	Subjects	McGill Pain Questionnaire (MPQ)					Visual Analogue Scale (VAS 0–10)			
		Total PRIRtot	Sensory %	Affective %	Evaluative %	Miscellaneous %	VAS <sub>1</sub>	VAS <sub>2</sub>	VAS <sub>3</sub>	VAS <sub>4</sub>
Headache	13	20.1 ± 4.3	30.5 ± 6.1	14.2 ± 5.2	31.0 ± 5.6	21.3 ± 5.4	1.0 ± 0.6	2.8 ± 0.7	4.9 ± 1.01	1.2 ± 0.66
Musculoskeletal	7	29.5 ± 5.4	43.5 ± 7.5	29.5 ± 9.1	51.4 ± 13.0	26.8 ± 8.8	4.6 ± 1.5	6.8 ± 1.5	7.2 ± 1.7	5.3 ± 0.9
Visceral referred	2	36 ± 5.0	53.5 ± 3.5	28.5 ± 14.3	30 ± 10.0	47 ± 11.8	1.5 ± 0.5	2 ± 0	6	6

Data refer to each kind of pain. MPQ. PRIRtot = Pain Rating Index rank Total. The total score is obtained summing the rank values of the adjectives chosen. Separate score for the sensory, affective, evaluative and miscellaneous classes is also computed for each class. The percentage with respect to maximum values has been calculated. VAS<sub>1</sub> = during the last 24 h VAS<sub>2</sub> = during the last week VAS<sub>3</sub> = during attacks VAS<sub>4</sub> = during the night.

acute pain episodes after the start of therapy. The same subjects did not reveal any change in the sensitivity to hot or cold temperatures.

#### 4. Discussion

In this study, we analyzed the effects on pain of cross-sex steroid administration in transsexuals. The main results indicate that sex steroid hormones not only have the expected sex-specific effects on the somatic characteristics of the subjects but also change their pain. About one-third of the male to female (MtF) subjects developed chronic pain concomitantly with estrogen/anti-androgen treatment, while about half of the female to male (FtM) subjects treated with testosterone reported a significant improvement of the chronic pain (headache) already present before the start of treatment. These findings support experimental data in animals and clinical data in humans suggesting that sex steroid hormones play an important role in pain.

The role of male or female steroid hormones in enhancing or reducing the development and maintenance of chronic pain has been shown in many animal models (see Craft et al., 2004). However, the extension of such research to human studies has been hindered by the lack of “experimental” models. In humans, the hormonal variations induced by common hormone treatments (birth control pills, HRT) are never very great, and the male or female gonadal hormones are given to the genetically appropriate sex, males or females, respectively, i.e. subjects who have experienced high levels of that kind of hormone throughout their life. In patients who have to drastically change their hormones (i.e. for breast or prostate cancer), it is difficult to study pain.

Therefore, transsexuals provide a unique opportunity to study human subjects who undergo a drastic change of their hormonal status as healthy adults (25–40 years); indeed, sex reassignments cannot be carried out before the age of majority. It must be stressed that although gender identity disorder is already present in adolescence, transsexuals are eugonadal before their sex reassignment (i.e. they have sex steroid concentrations and secondary sexual characteristics that are appropriate for their genetic sex). Moreover, the percentage of chronic pain

present before the hormone treatment recorded in this study (13/73, 17.8%) is similar to the values repeatedly reported in European countries, including the incidence of chronic pain in the two sexes (see Wiesenfeld-Hallin, 2005). Hence, it is not surprising that only a few of the males reported the presence of pain before the start of hormone treatment (MtF 3/47, 6%), while many of the females were already in pain (FtM 10/26, 38%). Likewise, it was not unexpected that the estrogen/anti-androgen treatment induced changes in pain sensitivity in a high number of MtF subjects, whereas the beginning of androgen treatment corresponded to an improvement of pain in the FtM subjects who suffered headache before the hormone treatment. These results confirm our working hypothesis, *but only partially*.

Indeed, although the hormone treatment was largely equivalent among subjects, there were individuals in each group who showed a clear change of their pain, while in other subjects the health condition did not change in spite of long-lasting hormone intake. The ability of hormone treatment to induce significant changes in these subjects was confirmed by the modifications observed in hormone serum levels and by the strong somatic changes occurring in all transsexuals. For instance, in the MtF subjects taking estrogens, the testosterone levels decreased to the normal ‘female’ range and serum estradiol increased to reach the steady-state level normally present in the pre-ovulatory and mid-luteal peaks in normal women (Becker et al., 2005). However, only about 1/3 of the subjects (29.8%) described here developed chronic pain.

These data suggest that the change from a male hormone environment to a female one exposed a ‘background’ (genetic?) condition able to induce a painful state. This condition was obviously already present before the start of treatment, but it became clinically relevant only after the hormonal change. Nevertheless, in view of the 70.2% of MtF subjects who did not develop any pain, it is evident that high estrogen levels alone are not able to induce pain.

To study pain, we used the McGill Pain Questionnaire (MPQ). The MPQ scores in the MtF group were high (PRIRtot: headache 53.4, musculoskeletal 29.3, visceral 42.0) compared to those reported by Gagliese and

Melzack (2003), who administered the full-scale MPQ to 278 patients suffering from different pain disorders (PRIrTot: 30). In particular, the *sensory and evaluative* components of headache were very high in our subjects (PRI: 74.2 and 76, respectively).

Patient self-evaluations of changes in pain are commonly utilised by clinicians and researchers (Marks et al., 1992) to estimate the efficacy of a treatment. This implies that patients remember the intensity of pain felt before and after the treatment, compare it to their current level of pain and operationally define the difference. The accuracy of this process is highly dependent on the accuracy of recollection. However, the reliability of memory for pain is still controversial and conflicting results have been reported (Erskine et al., 1990; Beese and Morley, 1993; Feine et al., 1998). For our subjects, the time before and after treatment was marked by the start of hormone intake. The changes involved the appearance of pain (if absent before), its magnitude (if already present) and the most common symptoms and signs associated with pain, including the impact of pain on the daily activity and of daily activity on the pain severity. In essence, the patients were required to reconstruct their pain experience and its context. The process of reconstruction is considered to enhance the accuracy of memory retrieval and thus its reliability (Rainville et al., 2004). The findings that emerged were consistent. That is, when hormone intake was accompanied by an improvement of pain, the associated signs and pain characteristics were weak, whereas when hormone intake was accompanied by a worsening of pain or its appearance, the features were sometimes dramatic.

Concerning the development of chronic headache, Pringsheim and Gooren (2004) suggested a direct effect of estrogens on peripheral mechanisms able to induce pain. In addition, several studies on the action of estrogens in central and peripheral sites suggested an overall involvement of the body (Boulware and Mermelstein, 2005). Estrogen receptors (ER) are present in almost all peripheral neural and non-neural structures and in most CNS circuits (Lanlua et al., 2001; Patchev et al., 2004). In particular, ER are present in the dermal and epidermal structures, and changes in estrogen plasma levels are able to modify the sensory characteristics of peripheral nerves, as shown (in agreement with the present results) by the enlargement of the peripheral receptor field and the decrease of the pain threshold in animals treated with these hormones (Bereiter et al., 1980; Bradshaw and Berkley, 2003). The higher incidence of pain in the MtF subjects after hormone treatment could be due not only to the pro-nociceptive effects of estrogens but also to the drop in their testosterone levels. In fact, pharmacological treatment of men with estrogens and anti-androgen induces a hypogonadal state (Morelli et al., 2004). While ER are commonly indicated as a CNS stimulant, androgen receptor (AR)-mediated actions

are often related to CNS inhibition. This inhibitory action has been invoked to explain the lower incidence of many forms of chronic pain in men (see Aloisi, 2003). Interestingly, the hypothesis of testosterone-mediated analgesia is only partially confirmed by the data from the other group of transsexuals, FtM. Most of these women were already in pain before the hormone treatment; however, although most of them benefited from the hormone intake (the number and length of pain attacks were significantly reduced), for some of them the pain features did not change and in others they worsened. These effects can be mediated by the AR modulation that occurs with hormone changes. For instance, ongoing testosterone treatment in FtM transsexuals is accompanied by upregulation of AR in peripheral tissues (van der Kwast et al., 1994).

To explain the breast pain and/or diffuse musculoskeletal pain present in almost all MtF subjects with chronic pain (13/14), we must remember that such pain is very common in women during the luteal phase of the menstrual cycle and different mechanisms have been proposed to explain its development (Wallace et al., 1996; Allen and McCarron, 2005). For example, the ability of estrogens to induce the production of TRPV1 in the intra-epidermal fibres has been shown in breast tissue (Gopinath et al., 2005); TRPV1 is the capsaicin or vanilloid receptor 1 required for thermal hyperalgesia in rodents. It was suggested that the abnormal intra-epidermal innervation found in women suffering breast pain reflects re-innervation of the skin following nerve stretch damage and/or collateral sprouting.

Finally, we cannot exclude that the pain changes reported by the transsexual subjects were related not only to changes in hormone levels but also to psychosociocultural aspects. Studies on the psychological aspects of these subjects have focused on the conformity to self-perceived gender, the presence of mental disorders and the motivations underlying the sex reassignment (Michel et al., 2001; Herman-Jeglinska et al., 2002). In general, the gender identification appears to match their request of sex reassignment, whereas the findings on the other aspects are variable. On the whole, a condition of anxiety and fear emerges from these investigations. Such a cognitive and emotional state might influence the severity of pain or its self-report, even though a true biological condition may substantially determine the intensity and incidence of pain.

## 5. Conclusion

Cross-sex hormone treatment influenced the occurrence and characteristics of pain in FtM and MtF transsexuals. These results may help to interpret the sex differences in pain and to clarify the potential benefits and risks of administration of exogenous steroids in general.

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